

**What proportion of patients with chronic heart failure are eligible for sacubitril–valsartan?**

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## **Abstract**

### **Aims**

The PARADIGM-HF trial showed that sacubitril–valsartan, an ARB–neprilysin inhibitor, is more effective than enalapril for some patients with heart failure (HF). It is uncertain what proportion of patients with HF would be eligible for sacubitril–valsartan in clinical practice.

### **Methods and results**

Between 2001 and 2014, 6131 patients consecutively referred to a community HF clinic with suspected HF were assessed. The criteria required to enter the randomized phase of PARADIGM-HF, including symptoms, NT-proBNP, and current treatment with or without target doses of ACE inhibitors or ARBs, were applied to identify the proportion of patients eligible for sacubitril–valsartan. Recognizing the diversity of clinical opinion and guideline recommendations concerning this issue, entry criteria were applied singly and in combination. Of 1396 patients with reduced left ventricular ejection fraction ( $\leq 40\%$ , HFrEF) and contemporary measurement of NT-proBNP, 379 were on target doses of an ACE inhibitor or ARB at their initial visit and, of these, 172 (45%) fulfilled the key entry criteria for the PARADIGM-HF trial. Lack of symptoms (32%) and NT-proBNP  $< 600$  ng/L (49%) were common reasons for failure to fulfil criteria. A further 122 patients became eligible during follow-up ( $n = 294$ , 21%). However, if background medication and doses were ignored, then 701 (50%) were eligible initially and a further 137 became eligible during follow-up.

### **Conclusions**

Of patients with HFrEF referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomization criteria, on which the ESC Guidelines are based; this proportion rises to 60% if background medication is ignored.

## Introduction

The treatment of chronic heart failure with reduced LVEF (HFrEF) with angiotensin-converting-enzyme (ACE) inhibitors is well established; for those who are unable to take ACE inhibitors, angiotensin receptor blockers (ARBs) are an alternative.[\[1\]](#) Beta-blockers and mineralocorticoid receptor antagonists also comprise part of standard ‘triple therapy’.[\[1\]](#) Recently a new class of agents, ARB–neprilysin inhibitors (ARNI), has been developed as an alternative to ACE inhibitors or ARBs. In the PARADIGM-HF trial, patients with HFrEF assigned to sacubitril–valsartan (LCZ696), the first compound in this new class, had a substantially lower rate of hospitalization for heart failure (HF) and mortality compared to those assigned to enalapril.[\[2, 3\]](#) However, patients were only eligible for randomization if they were stable, symptomatic, had an increased plasma concentration of natriuretic peptides, a systolic blood pressure  $\geq 100$  mmHg, and were able to tolerate both guideline-recommended doses of an ACE inhibitor (10 mg enalapril twice daily) and subsequently a target dose of sacubitril–valsartan (200 mg b.i.d.) during a run-in period.

As a consequence of the PARADIGM-HF results, the recently updated European Society of Cardiology (ESC) HF Guidelines recommend sacubitril–valsartan as a replacement for an ACE inhibitor only for patients similar to those randomized in the trial. Accordingly, we applied the entry criteria for the randomized phase of PARADIGM-HF to unselected patients referred to a community-based HF clinic to find the proportion appropriate for sacubitril–valsartan. Criteria were applied singly and in combination, recognizing the diversity of clinical opinion about how to apply the guidelines as well as differences among guidelines.

## Methods

### Study population

Between 2001 and 2014, consecutive referrals to a local hospital clinic, from both primary and secondary care physicians, were enrolled at a single clinic serving a local population of ~500 000 people (The Hull LifeLab). Patients were consented for the use of their medical information prior to investigation. Some patients had no prior diagnosis of HF and were treatment naïve, therefore requiring initiation of guideline-recommended therapy; others had a pre-existing diagnosis of HF and had already been initiated on treatment that might, however, require optimization.

Patients were reviewed by HF specialist nurses and doctors at regular intervals, usually at 4 and 12 months, and then annually, unless an appointment was requested sooner by the patient, physician, or specialist nurse. Information on demography, symptoms and signs, haematology, and biochemistry profiles (including NT-proBNP), ECGs, and echocardiograms were systematically recorded at each time point in a dedicated electronic health record stored on a secure NHS server. Titration of treatment was co-ordinated by the clinic but often implemented by community HF nurses or general practitioners.

For the present analysis, we focused only on patients with HF who had a baseline echocardiographic LVEF  $\leq 40\%$  (or moderate or severe LV systolic dysfunction by visual estimation if LVEF could not be calculated) and a contemporary measurement of plasma NT-proBNP. We used data from the initial assessment and the 4- and 12-month follow-up visits, at which time we expected titration of medication to be complete.

In PARADIGM-HF, patients had to fulfil selection criteria for both screening and randomization, but symptom, natriuretic peptide, and LVEF criteria only had to be fulfilled at screening, and target doses of ACE inhibitors/ARBs only had to be fulfilled prior to randomization. The ESC Guidelines use five criteria to recommend eligibility for sacubitril-valsartan: symptoms, natriuretic peptide, LVEF, estimated glomerular filtration rate (eGFR; which was measured both at screening and at randomization), and ACE inhibitor/ARB dose. We adopted a similar mixed approach to eligibility but also report how each individual criterion affected eligibility.

Patients were classified as being ‘on target dose’ or ‘not on target dose’ of ACE inhibitors or ARBs (using the criteria for entering the randomized phase of PARADIGM-HF, consistent with ESC Guidelines (i.e. enalapril 20 mg daily, or equivalent; [Table 1](#)).<sup>[2]</sup> In line with eligibility to enter the screening phase of PARADIGM-HF and ESC Guidelines, patients who were either asymptomatic (NYHA class I) or did not have HFrEF or an elevated NT-proBNP were excluded. PARADIGM-HF allowed inclusion with values of  $>600$  ng/L or  $400\text{--}600$  ng/L if the patient had been hospitalized for HF in the previous year. We did not have such data for this analysis and therefore show data for NT-proBNP using both thresholds. The hospitalization criterion may change during follow-up in clinical practice and therefore it is appropriate to show the more liberal criterion of 400 ng/L even in the absence of hospitalization data. Other exclusion criteria at screening were simultaneous prescription of both an ACE inhibitor and an ARB; systolic blood pressure (SBP)  $<100$  mmHg; eGFR

<30 mL/min/1.73 m<sup>2</sup>; serum potassium (K) >5.2 mmol/L; significant aortic or mitral valve disease; and significant liver disease (see Supplementary material online, *Table S1* for more detailed inclusion and exclusion criteria). We defined ‘future potential candidates’ as those not on target ACE inhibitors or ARBs, who might fulfil criteria for eligibility if they were on target doses.

Patients qualifying for randomization had to meet slightly different cut-offs for SBP ( $\geq 95$  mmHg) and serum K ( $\leq 5.4$  mmol/L) than those used at the screening visit. We therefore also report the proportion of patients meeting these criteria.

We also assessed how many patients might be eligible for sacubitril–valsartan assuming that it might be given regardless of background therapy, including beta-blockers and/or ACE inhibitors or ARBs, and regardless of plasma NT-proBNP. We also report the proportion of patients taking doses of ACE inhibitors/ARBs required to enter the screening phase (equivalent to 10 mg/day of enalapril) who were otherwise eligible for sacubitril–valsartan.

Echocardiograms and measurements of NT-proBNP, K, and creatinine were not always repeated at follow-up, in which case the most recent test result was used.

For patients not on target dose of ACE inhibitors or ARBs at 12 months, medical records were reviewed by three doctors to try to identify reasons for failed up-titration.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent for their data to be used for research.

### **Statistical analysis**

Categorical data are presented as number and percentages; normally distributed continuous data as mean  $\pm$  standard deviation (SD); and non-normally distributed continuous variables as median and interquartile range (IQR). One-way analysis of variance (ANOVA) and Kruskal–Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the  $\chi^2$  test was used for categorical variables. All analyses were performed using SPSS (v.22) software. A two-sided *P*-value <0.05 was considered statistically significant.

## Results

### All patients at baseline assessment

Of 6131 consecutive referrals with suspected HF between 2001 and 2014, the diagnosis was confirmed in 3637, of whom 1980 had a reduced LVEF (HFrEF). Data were incomplete for 584 patients, mostly because of missing measurements of plasma NT-proBNP (Supplementary material online, *Figure S1*), leaving 1396 patients with HFrEF and a contemporaneous measurement of NT-proBNP; of these, 379 (27%) were already on target dose of an ACE inhibitor or ARB (*Table 2*; *Figure 1*).

Venn diagram showing the number of patients eligible for sacubitril–valsartan following the strict criteria used in the PARADIGM-HF trial. The orange box shows cumulative, unique patients. ACE-I, ACE inhibitor; FU, follow-up.

### Patients on target ACE inhibitor or angiotensin receptor blocker dose at baseline

Of 379 patients (27%) on target dose of an ACE inhibitor or ARB at baseline, just under half ( $n = 172$ , 45%; 12% of the overall population) fulfilled criteria for sacubitril–valsartan. If the criteria for entering the randomization phase of PARADIGM-HF are used to define the patient group ( $K \leq 5.4$  mmol/L and  $SBP \geq 95$  mmHg), then a further 16 patients would have been eligible for sacubitril–valsartan (8 patients had  $SBP$  95–99 mmHg, but 3 had other contraindications, and 15 patients had  $K = 5.3$ – $5.4$  mmol/L, of whom 4 had other contraindications).

Lack of limiting symptoms (32%) and plasma NT-proBNP  $< 600$  ng/L (49%) were the most common reasons for failing to fulfil eligibility criteria; 28% failed for two or more reasons. Patient characteristics are summarized in *Table 2*.

Patients fulfilling the eligibility criteria for sacubitril–valsartan were older, had more clinical signs of congestion, were prescribed higher doses of loop diuretics, had larger left atrial diameter, had a higher heart rate, and were less likely to be in sinus rhythm.

### Patients not on target ACE inhibitor or angiotensin receptor blocker dose at baseline

Of 1017 patients not on target dose of an ACE inhibitor or ARB at baseline, 529 (52%) were considered future candidates (38% of the overall population) for sacubitril–valsartan (*Table*

2) if titration of an ACE inhibitor/ARB was successful. Of the 529 future candidates, 178 were on  $\geq 50\%$  of target doses of an ACE inhibitor or ARB, while 351 were taking  $< 50\%$  of target dose or were not prescribed these medicines. Those considered future potential candidates were older, more likely to be women, had more peripheral oedema, worse renal function, a higher heart rate, and were more likely to be in AF.

Among the 488 not thought to be future candidates, absence of limiting symptoms (30%), plasma NT-proBNP  $< 600$  ng/L (33%), SBP  $< 100$  mmHg (20%), and eGFR  $< 30$  mL/min/1.73 m<sup>2</sup> (16%) were the most common reasons for classifying the patients as unlikely to be eligible for sacubitril–valsartan even if ACE inhibitors/ARBs could be titrated; 25% of patients were excluded for two or more criteria.

#### **Four-month assessment**

Between the initial and 4-month assessments, 97 patients died and 147 did not attend their scheduled visit. Of 1152 who attended, 446 (39%) patients were on target doses of ACE inhibitors/ARBs but only 149 fulfilled the eligibility criteria for sacubitril–valsartan (*Table 3*). Of the 863 patients who had an echo at the 4-month visit, 211 (24%) had an improved LVEF to  $> 40\%$ . Recovery in LVEF to  $> 40\%$  ( $n = 94$ ; 26% of the 355 with an updated echocardiogram; we assumed LVEF had not changed in 91 patients who had no repeat echocardiogram), lack of limiting symptoms (36%) and plasma NT-proBNP  $< 600$  ng/L (49%) were the most common reasons for classifying patients receiving target doses of ACE inhibitor/ARB as ineligible for sacubitril–valsartan; 44% were excluded for two or more reasons.

When we applied the SBP and K criteria used for the randomized phase, the number of patients eligible at this visit increased to 166 (13 patients had SBP 95–99 mmHg, but 5 had other contraindications, and 12 patients had K = 5.3–5.4 mmol/L, of whom 3 had other contraindications).

#### **Patients not on target ACE inhibitor or angiotensin receptor blocker dose at 4-month assessment**

Of the 706 patients not on target dose of ACE inhibitors or ARBs at 4-month follow-up, 278 were still considered to be potential candidates for sacubitril–valsartan (Supplementary

material online, *Table S2*). Absence of limiting symptoms (27%), NT-proBNP <600 ng/L (36%), recovery in LVEF to >40% ( $n = 117$ ; 23% of the 508 patients with an updated echocardiogram), and low SBP (17%) were other common reasons for not fulfilling criteria for sacubitril–valsartan.

### **Twelve-month assessment**

A total of 162 patients died prior to the 12-month assessment and 196 failed to attend. Of the 979 patients who had an echo either at the 4-month ( $n = 276$  carried forward) or at the 12-month visit ( $n = 703$ ), 304 (31%) had improved their LVEF to >40%, including 6 patients who died after 4 months and 18 who did not attend. Of 1038 patients who attended, 453 (44%) were on target doses of ACE inhibitors or ARBs.

Of the 453 patients titrated to target doses of ACE inhibitors or ARBs, only 127 (28%) fulfilled the criteria for sacubitril–valsartan (*Table 3*).

Recovery in LVEF to >40% ( $n = 134$ ), lack of limiting symptoms (35%), and plasma NT-proBNP <600 ng/L (52%) were the most common reasons for classifying the patients as ineligible for sacubitril–valsartan; 47% were excluded for two or more reasons.

Of the 585 patients not on target dose of ACE inhibitors or ARBs at the 12-month follow-up visit, 192 (33%) were still considered to be potential candidates for sacubitril–valsartan (Supplementary material online, *Table S3*). Absence of limiting symptoms (30%), NT-proBNP <600 ng/L (41%), recovery in LVEF to >40% ( $n = 146$ ), and low SBP (15%) were other common reasons for failing to meet criteria for sacubitril–valsartan.

When the SBP and K criteria for the randomization phase were applied, the number of patients eligible at this visit increased from 127 to 150 (18 patients had SBP 95–99 mmHg, but 2 had other contraindications, and 8 patients had  $K = 5.3$ – $5.4$  mmol/L, of whom 1 had other contraindications). Thus, there would thus have been 340 (24%) rather than 294 (21%) patients with HFrEF eligible for sacubitril–valsartan on at least one occasion.

### **Missing up-titration**

Overall, 625 (45%) patients achieved target doses of ACE inhibitors/ARBs on at least one occasion, compared with 27% at the initial visit. Of the 585 not on target ACE



inhibitors/ARBs at the 12-month visit, there was no obvious reason for failure to up-titrate in 271 cases (46%); up-titration was still ongoing in 100 cases (17%) or had been prevented by symptomatic hypotension (12%) or worsening renal function (12%) (*Figure 2*).

Diagram showing reasons for missing up-titration in patients not on target ACE inhibitor (ACE-I) or ARB at the 12-month visit. HF, heart failure.

### **All patients taking at least 50% of target ACE inhibitor or angiotensin receptor blocker dose**

Further analysis was done in order to evaluate if, and how, a lower dose of ACE inhibitors/ARBs (equivalent to 50% of the target dose of enalapril, as required for entry into the PARADIGM-HF trial, rather than the target dose required for the randomization phase of the PARADIGM-HF[2]) would have affected the proportion of patients with HFrEF eligible for sacubitril–valsartan. Of patients prescribed at least 50% of target ACE inhibitor or ARB dose, 350 (25%) patients fulfilled criteria for sacubitril–valsartan at baseline, rising to 504 (36% of surviving attenders) at 4 months and 594 (43% of surviving attenders) by 12 months.

### **All patients regardless of background therapy and natriuretic peptide plasma levels**

If criteria for eligibility were extended to all 1396 patients regardless of background treatment, 701 (50%) were potentially eligible for sacubitril–valsartan at baseline (*Figure 3*). During follow-up, the overall number of patients eligible for sacubitril–valsartan decreased, mainly due to improvement in symptoms and LVEF, and reductions in NT-proBNP. Ignoring background medication, 838 (60%) unique patients might have been eligible for sacubitril–valsartan on at least one visit.

Venn diagram showing the number of patients eligible for sacubitril–valsartan following the criteria used in the PARADIGM-HF trial, regardless of background therapy. The orange box shows cumulative, unique patients. FU, follow-up.

If neither NT-proBNP nor ACE inhibitors/ARBs were considered as criteria for eligibility, 877 (63%) patients would have been eligible initially. The number of potentially eligible patients at any time during 1-year follow-up was 1139 (81% of the total population); this includes 253 patients who were naïve to, or had not tolerated, ACE inhibitors or ARBs at the time of consideration.

## One-year mortality

Of patients fulfilling strict criteria for eligibility for sacubitril–valsartan in our analysis, 1-year mortality was 8.7%. This compares with 1.5% in those excluded because NT-proBNP was <400 ng/L and with 2.0% when NT-proBNP was <600 ng/L. For patients excluded because of contraindications, the 1-year mortality was 13.3%. When more liberal criteria (eligibility regardless of background therapy, including beta-blockers and ACE inhibitors or ARBs) were applied, 1-year mortality was 10.8% in patients otherwise eligible for sacubitril–valsartan. This compares with 2.3% in those excluded because NT-proBNP was <400 ng/L and with 3.0% when NT-proBNP was <600 ng/L. For patients excluded because of contraindications, the 1-year mortality was 18.2% (*Figure 4*).

Histograms showing the 1-year mortality of patients considered eligible for sacubitril–valsartan, of those with low NT-proBNP (<400 ng/L and 600 ng/L), and of those considered to have contraindications to sacubitril–valsartan use. Two clinical situations have been considered, the first in patients who were on target dose of ACE inhibitor (ACE-I) or ARB (A), the second in patients regardless of background heart failure therapy (B).

Contraindications include: significant valvular disease, systolic blood pressure <100 mmHg, alanine aminotransferase >2 times normal value, serum potassium >5.2 mmol/L, concurrent prescription of ACE-I/ARB, and an estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>. HFrEF, heart failure with reduced ejection fraction.

## Discussion

It could be argued that only patients whose disease has not been controlled by an adequate trial of ACE inhibitors/ARBs and who still have a substantial increase in risk should be considered for a new and potentially costly treatment.[4] If the entry criteria for the PARADIGM-HF trial are strictly followed, sacubitril–valsartan should be prescribed to <25% of patients with HFrEF referred to (and followed up in) a community HF clinic. This not only reflects the relatively low proportion of patients who achieve guideline target doses of ACE inhibitors or ARBs in clinical practice due to problems such as renal dysfunction or hypotension, but also suggests failure of doctors and nurses to recommend or implement titration, or unwillingness of patients to comply, as well as the substantial proportion of patients who either have few symptoms or who do not have elevated plasma concentrations of natriuretic peptides once treated.

The evidence for prescribing ACE inhibitors in patients with HFrEF is clear. However, even though prescription rates have improved over the last 15 years, many patients are not titrated up to the target doses advocated in guidelines.[\[5\]](#) The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE-HF) prospectively tested a multidimensional, performance improvement intervention in >15 000 patients with HFrEF in the USA.[\[6\]](#) Only 38% achieved target doses of ACE inhibitors/ARBs in the 24 months after intervention; an improvement of only 2% on the pre-intervention rate.[\[7\]](#) In Denmark, a study of >100 000 patients discharged after a first hospitalization for HF found that although 79% of patients were still on renin–angiotensin inhibitors 5 years after initiation of treatment, the doses of ACE inhibitors were substantially lower than the target dose and similar to those at the time of discharge.[\[8\]](#) Among 5000 patients with HFrEF in the ESC HF Long-Term Registry, only 28% were receiving target doses of ARBs or ACE inhibitors. Common reasons for not being at target were ongoing up-titration and side effects, such as symptomatic hypotension and/or worsening renal function, but for many patients there was no obvious reason.[\[9, 10\]](#) This is similar to the experience in our own clinic. Whether audit and education can improve implementation any further than in our clinical practice remains to be demonstrated.

A recent retrospective analysis of the PARADIGM-HF study showed that >40% of patients had doses of trial medication down-titrated during follow-up, but this was not associated with a loss of the advantage of sacubitril–valsartan over enalapril for morbidity and mortality.[\[11\]](#) This suggests that a lower dose of sacubitril–valsartan might be superior to lower than target doses of ACE inhibitors/ARBs. However, it is important to remember that all these patients passed the initial run-in phase and had thus received target doses of enalapril and sacubitril–valsartan before the doses were subsequently decreased (due, for example, to hypotension or hyperkalaemia). There remains some uncertainty as to whether sacubitril–valsartan is superior to ACE inhibitors in patients unable to tolerate guideline-recommended doses in the first place.

We found that a common reason for not meeting criteria for sacubitril–valsartan was improvement in symptoms, LVEF, and NT-proBNP with conventional therapy following initiation of treatment. Data from American and European registries suggest that about one-third of patients with HFrEF have a substantial improvement in LV systolic function with guideline-indicated treatments,[\[12–14\]](#) especially for patients with dilated cardiomyopathy

who are less likely to have extensive myocardial scar.[[15, 16](#)] We do not know if sacubitril–valsartan will be superior to enalapril in patients whose disease is well controlled on current standard treatment. Although patients had to be symptomatic to enter screening, 5% were asymptomatic by the end of run-in, but this is too small a sample to provide definitive guidance. Even if the relative benefit is similar in this subgroup of patients, the absolute benefit of treatment is likely to be small and may not be cost-effective.

The PARADIGM-HF trial was designed to prove the concept that ARNIs were superior to ACE inhibitors and was not a pragmatic trial designed primarily to inform clinical practice. If it is accepted that ARNIs are superior to ACE inhibitors then, rather than going to the trouble of titrating patients to full dose ACE inhibitor and then switching to an ARNI, it may be appropriate to initiate patients on the latter from the outset. HFrEF is fundamentally a malignant disease and it is reasonable to consider that the best treatment should be applied from the point of diagnosis in all patients at increased risk. From this perspective, ARNIs, rather than ACE inhibitors, could be considered the first-line treatment for HFrEF. If so, this greatly expands the proportion of patients with HFrEF who are eligible for sacubitril–valsartan.

Sacubitril–valsartan might be less well tolerated in those naïve to the drug.[[17, 18](#)] During the run-in phase of PARADIGM-HF, 10% of patients did not tolerate the target dose of sacubitril–valsartan even among patients who tolerated enalapril 10 mg b.i.d.[[2](#)] Moreover, patients had to be on stable medication for up to 2 months before randomization. The safety of initiating sacubitril–valsartan in ACE inhibitor-naïve patients or those with recent decompensation, including those with incident HF, is uncertain.

Previous and current European guidelines do not recommend routine treatment with ACE inhibitors in patients with HFrEF and impaired renal function (creatinine  $>221 \mu\text{mol/L}$  or  $\text{eGFR} \leq 30 \text{ mL/min/1.73 m}^2$ );[[1, 19](#)] whether sacubitril–valsartan is safe and effective in this scenario also requires further investigation.

Three major regulatory authorities [the Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the National Institute for Health and Care Excellence (NICE)] have not suggested that initiation of sacubitril–valsartan should be restricted to patients with an elevated NT-proBNP. We believe this is a mistake. Natriuretic peptides are powerful prognostic markers. Low values will identify patients at low risk in whom

sacubitril–valsartan is unlikely to be cost-effective. Even if the relative reduction in risk is similar, patients at low risk of events will have a small absolute benefit.

The PARADIGM-HF trial mostly included patients who were very stable. Patients and their doctors may be reluctant to change therapy when symptoms are mild and the patient has had no recent events. Most patients with mild symptoms would not notice much difference after changing therapy; the doctor knows this. Some patients will have adverse events after changing therapy, which will be blamed on the new treatment whether or not it is the reason; the doctor knows this. Prescribing inertia, which is associated with short-term safety but long-term risk, must somehow be overcome. Educating doctors and patients to change prescriptions is likely to be facilitated by a test indicating that although the patient appears symptomatically to be ‘doing quite well’ their underlying disease is not yet under control. The cost of measuring natriuretic peptides is similar to that of a few days' treatment with sacubitril–valsartan. In our opinion, measuring plasma natriuretic peptides would be a simple, effective and probably cost-effective strategy that would reduce prescriptions of sacubitril–valsartan for patients who had little to gain and greatly increase them in those most likely to benefit. We predict that this would lead to an overall increase in sacubitril–valsartan use but, importantly, a greater increase in what we consider appropriate use.

## **Limitations**

The analysis should be considered a snapshot at three time intervals, and not a complete picture of the natural history of the disease in this group of patients.

Some might argue about the representativeness of our cohort and generalizability of our findings: however, our HF clinic accepts consecutive referrals from multiple sources, without any exclusion criteria (thus, for example, patients with previous or current diagnosis of cancer, with severe renal failure, or undergoing renal dialysis are all accepted). Our study was conducted in secondary care; patients managed solely in primary care are likely to differ but, in our region, are unlikely to receive the diagnostic tests that would qualify them for sacubitril–valsartan. The population enrolled in our study was much older than that enrolled in PARADIGM-HF, and is thus far more representative of ‘real-world’ clinical practice. However, as in PARADIGM-HF, the population we serve is predominantly of European descent with few people of Asian, African, or American origin.

For the purpose of the analysis, we used patients with a complete baseline data set, including NT-proBNP and echocardiography; the proportion of eligible patients might have been different in those with incomplete data. Data collection was also incomplete during follow-up visits, reflecting current clinical practice; some patients did not attend all clinical visits, or did not have NT-proBNP or LVEF reassessed at every follow-up. We included patients with an LVEF  $\leq 40\%$  but the entry criteria for PARADIGM-HF were changed to include only patients with LVEF  $\leq 35\%$  during the course of the study. This change was implemented to try to increase events and because investigators, trying to increase recruitment, tend to bias their measurement of LVEF.[\[20\]](#) There is no similar reason for bias in our cohort as all referred patients are enrolled regardless of LVEF. Restriction of sacubitril–valsartan only to patients with an LVEF  $\leq 35\%$  would have further reduced the proportion eligible (for instance, from 172 to 107 of those eligible at baseline).

We started enrolment of this cohort in 2001. Since then, there have been changes in recommended treatments for HFrEF, including CRT when QRS duration is prolonged, ivabradine for those in sinus rhythm with higher heart rates despite the use of beta-blockers, and extension of the indication for mineralocorticoid receptor antagonists to patients with mild symptoms.[\[1, 19\]](#) Such treatment applied to patients from the earlier part of our cohort might increase the number of patients with improved LV function, fewer symptoms, and lower natriuretic peptides, thus decreasing the proportion of patients eligible for sacubitril–valsartan.

## Conclusions

Sacubitril–valsartan is an important advance in the management of patients with HFrEF. Some preliminary reports give widely differing views on the proportion of patients eligible for sacubitril–valsartan,[\[21, 22\]](#) which might reflect the criteria applied and the lack of detailed patient information. Our highly granular data emphasize the importance of showing more than one scenario. If the selection criteria for PARADIGM-HF are strictly applied,  $<25\%$  of patients with HFrEF might be eligible for switching to sacubitril–valsartan. The proportion of patients with HFrEF eligible for sacubitril–valsartan increases substantially if it is considered an agent of first choice in preference to an ACE inhibitor for patients with HFrEF and an adverse risk profile, and increases even further if natriuretic peptide plasma levels are not considered, with up to 81% of patients with HFrEF potentially eligible at some point. If the prevalence of HF is considered to be 1% and half of these patients have

HFrEF,[[23](#), [24](#)] then, assuming our data are representative of other regions, somewhere between 65 000 (conservative estimate) and 200 000 (liberal estimate) patients in the UK (population ~65 million) might be eligible for sacubitril–valsartan, between 500 000 and 1.5 million in current European Union countries (population ~500 million), and between 320 000 and ~1 million in the USA (population ~320 million).

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